Pluripotent and Somatic Stem Cell Models to Study Inherited Diarrheal Disorders

Grant Award Details

Pluripotent and Somatic Stem Cell Models to Study Inherited Diarrheal Disorders

Grant Type: Tools and Technologies II

Grant Number: RT2-01985

Project Objective: 1)Generate iPS-derived intestinal epithelium in culture and ex vivo from subjects with various inherited diarrheal disorders.
2)Develop methods to grow human small bowel epithelium in culture or ex vivo from somatic stem cells of normal subjects, and those with inherited diarrheal disorders.

Investigator:

Name:	Martin Martin
Institution:	University of California, Los Angeles
Type:	PI

Disease Focus: Genetic Disorder, Intestinal Disease, Metabolic Disorders, Pediatrics

Human Stem Cell Use: iPS Cell

Cell Line Generation: iPS Cell

Award Value: $1,783,250

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Reporting Period: NCE (Year 4)

View Report

Grant Application Details

Application Title: Pluripotent and Somatic Stem Cell Models to Study Inherited Diarrheal Disorders

Public Abstract:

Our research group at [REDACTED] has had a long-standing interest in understanding the cause of several disorders that result in severe, and often times fatal forms of diarrhea in children. These diarrheal disorders are inherited, and somehow lead to poor absorption of nearly all forms of nutrients, including protein, sugars and fats. Why children with these disorders have impaired absorption of nutrients is one of the main unsolved mysteries, but they generally require life-long the daily infusion of intravenous nutrients or an intestinal transplantation to sustain proper growth and nutrition.

The goal of this grant application is to develop personalized disease-in-a-dish models that can be used to solve these and other gastrointestinal disorders that are poorly understood. Specifically, we propose to develop custom-made "diarrhea-in-a-dish" models that will use pluripotent stem (iPS) cells derived from skin biopsies of individuals with various forms of diarrhea. These iPS cells will be induced to form gut epithelium that we believe will resemble various characteristics of the subjects native intestine. We will also develop methods that are already established in mice, to isolate and expand human intestinal (somatic) stem cells in cell incubators and in fat compartments of immunodeficient mice. We believe that the resulting intestinal units can be manipulated using various commonly used tools to introduce and/or suppress genes that might control the histology and function of the gut.

We are also using newly developed genetic tools where the entire important (coding) region of the human genome is sequenced to identify genes that are defective, and thereby may account for the diarrheal disorder under investigation. This new approach generally identifies several genes that are defective, and we propose to introduce the normal forms of these various genes into the stem cell derived gut tissue to see which gene might reverse the abnormality. We believe that the combination of these various approaches will likely assist us in defining the cause of various forms of diarrhea.

While short-term bouts (acute) of diarrhea are very common, approximately 5% individuals experience chronic (>2 weeks) diarrheal symptoms, and some may be life-long. Unfortunately, Physicians and Scientist alike have a very poor understanding of why so many patients experience chronic diarrhea. While the congenital diarrheal disorders under investigation in this grant are rare conditions, improving our understanding of these types of genetic disorders will undoubtedly provide new insight into how nutrients are absorbed, and may enhance our understanding of several common but poorly understood disorders, including IBD, IBS, drug-induced and other idiopathic forms of chronic diarrhea. Developing, refining and expanding the tools described here may also set the foundation to study other common disorders, and to screen for novel drug discovery.

Statement of Benefit to California:	Chronic diarrheal disorders are common aliments among Californians, and result in frequent and prolonged hospitalizations, outpatient doctor visits and lost wages from sick leave. A subset of young children develop diarrhea shortly after birth, and some will require either daily life-long intravenous nutrition and/or intestinal transplantation. While the medical cost incurred from all forms of chronic diarrhea is daunting, we have a very poor understanding of the basis of most diarrheal conditions, and currently available drug therapies have limited efficacy. In this grant application, we propose to use pluripotent and somatic stem cells to assist us in solving the cause of several forms of congenital diarrheal disorders. We believe that these "diarrhea-in-a-dish models" can be used in the future to understand the cause of other common forms of diarrhea, and to screen for potential drug targets. Furthermore, the approaches taken here may provide alternative advances to small bowel transplantation in these more difficult cases of chronic diarrhea. Public and private insurers spend hundreds of millions of dollars in the diagnosing and management of children and adults with various forms of chronic diarrhea. More importantly, patients and their families are frequently immersed in the consequences of suffering from chronic aliments that are debilitating, hamper quality of life, and require frequent medical attention. Given our incomplete understanding of these conditions, the limited therapeutic options available, and the direct and indirect cost to the state of California and its citizens, novel approaches only recently available with the use of stem cell technology may provide new insight, and possible solutions and hope for those affected by these conditions.

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